Transmission Dynamics: Role of Asymptomatic Cases

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

N Engl J Med 2009;360:2536-43.

Zika Virus Outbreak on Yap Island, Federated States of Micronesia

Mark R. Duffy, D.V.M., M.P.H., Tai-Ho Chen, M.D., W. Thane Hancock, M.D., M.P.H., Ann M. Powers, Ph.D., Jacob L. Kool, M.D., Ph.D., Robert S. Lanciotti, Ph.D., Moses Pretrick, B.S., Maria Marfel, B.S., Stacey Holzbauer, D.V.M., M.P.H., Christine Dubray, M.D., M.P.H., Laurent Guillaumot, M.S., Anne Griggs, M.P.H., Martin Bel, M.D., Amy J. Lambert, M.S., Janeen Laven, B.S., Olga Kosoy, M.S., Amanda Panella, M.P.H., Brad J. Biggerstaff, Ph.D., Marc Fischer, M.D., M.P.H., and Edward B. Hayes, M.D.

- 18% of those infected (10-27%) had a clinical illness that was probably attributable to ZIKV

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

This article was published on March 4, 2016, at NEJM.org.

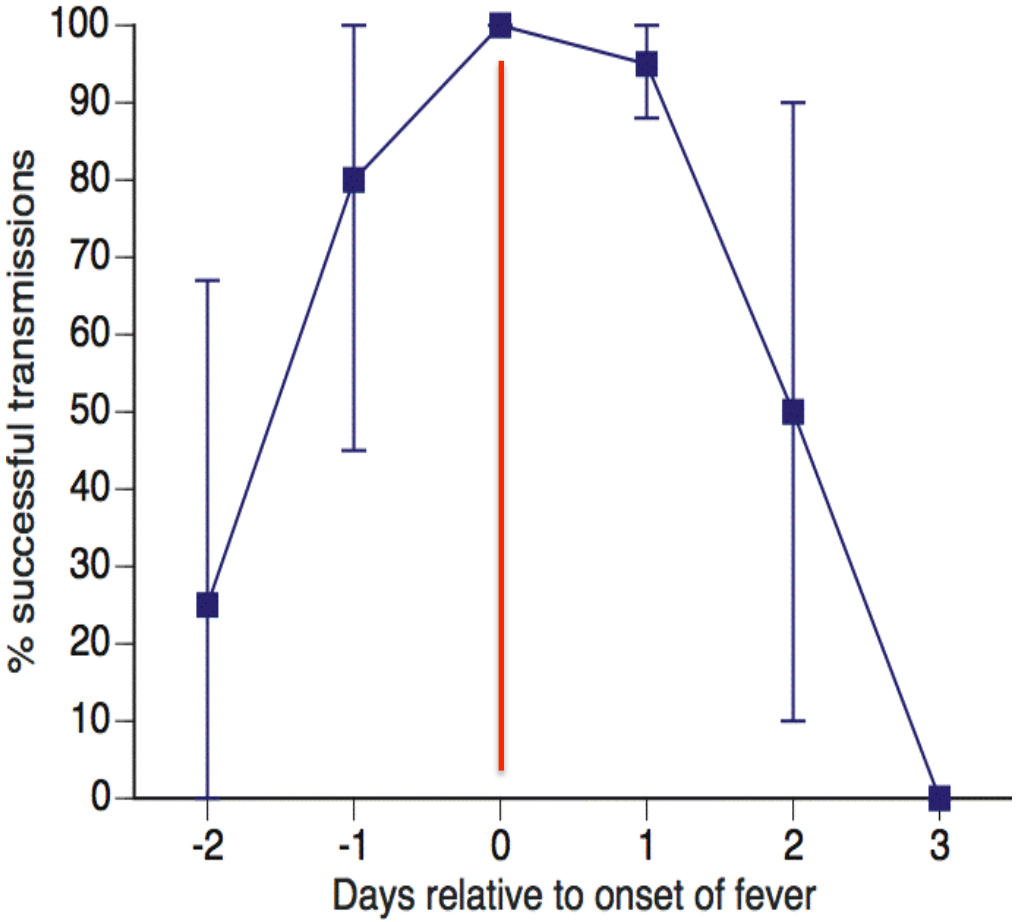
Zika Virus Infection in Pregnant Women in Rio de Janeiro — Preliminary Report

Patrícia Brasil, M.D., Jose P. Pereira, Jr., M.D., Claudia Raja Gabaglia, M.D., Luana Damasceno, M.S., Mayumi Wakimoto, Ph.D., Rita M. Ribeiro Nogueira, M.D., Patrícia Carvalho de Sequeira, Ph.D., André Machado Siqueira, M.D., Liege M. Abreu de Carvalho, M.D., Denise Cotrim da Cunha, M.D., Guilherme A. Calvet, M.D., Elizabeth S. Neves, M.D., Maria E. Moreira, M.D., Ana E. Rodrigues Baião, M.D., Paulo R. Nassar de Carvalho, M.D., Carla Janzen, M.D., Stephanie G. Valderramos, M.D., James D. Cherry, M.D., Ana M. Bispo de Filippis, Ph.D., and Karin Nielsen-Saines, M.D.

CONCLUSIONS

Despite mild clinical symptoms, ZIKV infection during pregnancy appears to be associated with grave outcomes, including fetal death, placental insufficiency, fetal growth restriction, and CNS injury.

Human-to-Mosquito DENV Transmission: Experimentally Infected People

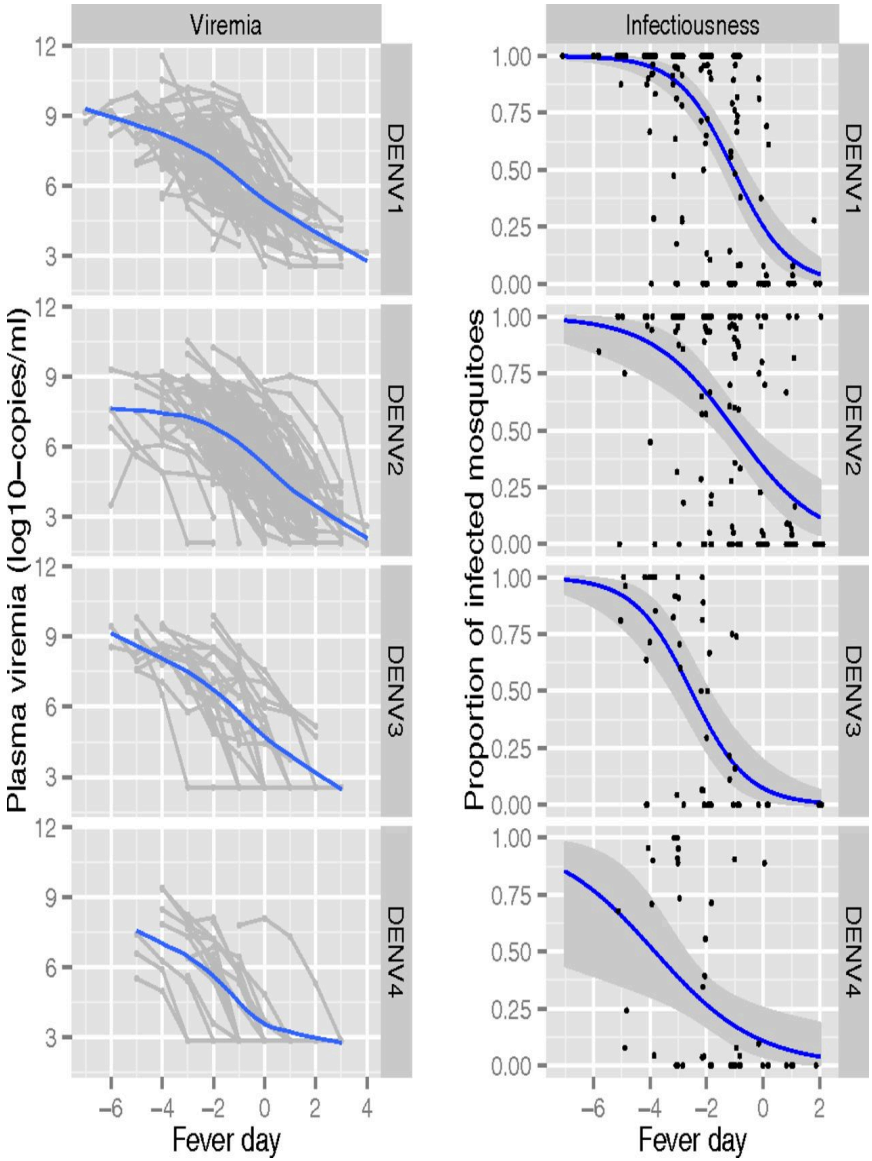


DENV-4 infectious period in symptomatic humans. Percentage of exposed *Ae. aegypti* that transmitted virus to human volunteers (95% CI).

- Adapted from Nishiura & Halstead *J Infect Dis* 2007 following reanalysis of Siler et al. *Philipp J Sci* 1926

- Small cohorts of human volunteers
- Only overt disease considered
- Disease onset after 4-9 days of intrinsic incubation
- Successful transmission after ≥11 days of extrinsic incubation

Human-to-Mosquito DENV Transmission: Naturally Infected People



- 208 hospitalized patients in Vietnam
- Few transmission events after defervescence (fever day=0)
- Infectiousness to mosquitoes up to 6th day after symptom onset
- Transmission probability was associated with viremia profile

PNAS

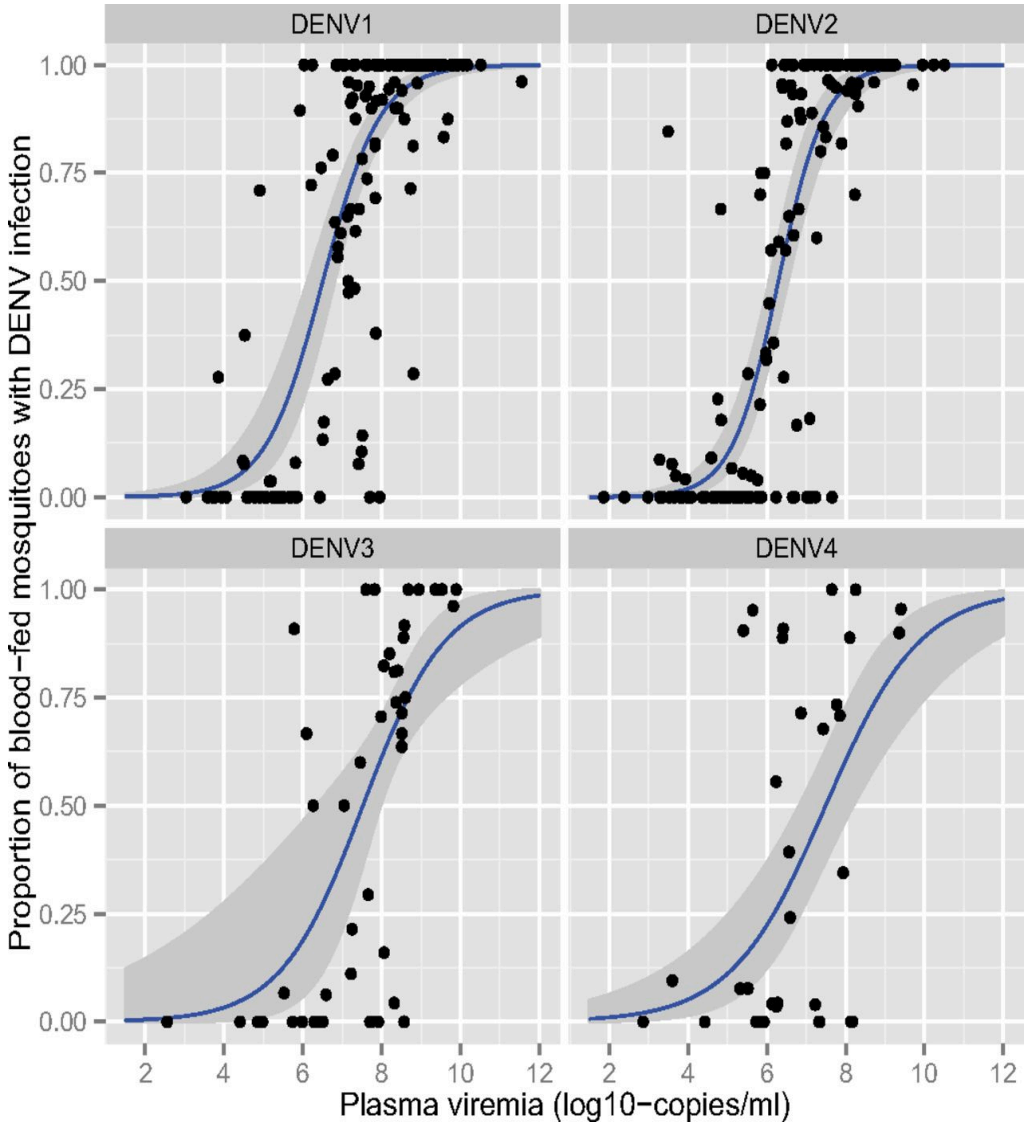
Host and viral features of human dengue cases shape the population of infected and infectious *Aedes aegypti* mosquitoes 2013

Nguyet Minh Nguyen[a], Duong Thi Hue Kien[a], Trung Vu Tuan[a], Nguyen Than Ha Quyen[a], Chau N. B. Tran[a], Long Vo Thi[a], Dui Le Thi[a], Hoa Lan Nguyen[a], Jeremy J. Farrar[a,b], Edward C. Holmes[c,d], Maia A. Rabaa[a], Juliet E. Bryant[a,b], Truong Thanh Nguyen[e], Huong Thi Cam Nguyen[e], Lan Thi Hong Nguyen[e], Mai Phuong Pham[e], Hung The Nguyen[e], Tai Thi Hue Luong[e], Bridget Wills[a,b], Chau Van Vinh Nguyen[e], Marcel Wolbers[a,b], and Cameron P. Simmons[a,b,f,1]

Infectiousness and Viremia are Strongly, Positively Correlated

Dose-responses of 208 hospitalized dengue patients in Vietnam

DENV-1
OID_{50}= 6.51



DENV-2
OID_{50}= 6.29

DENV-3
OID_{50}= 7.52

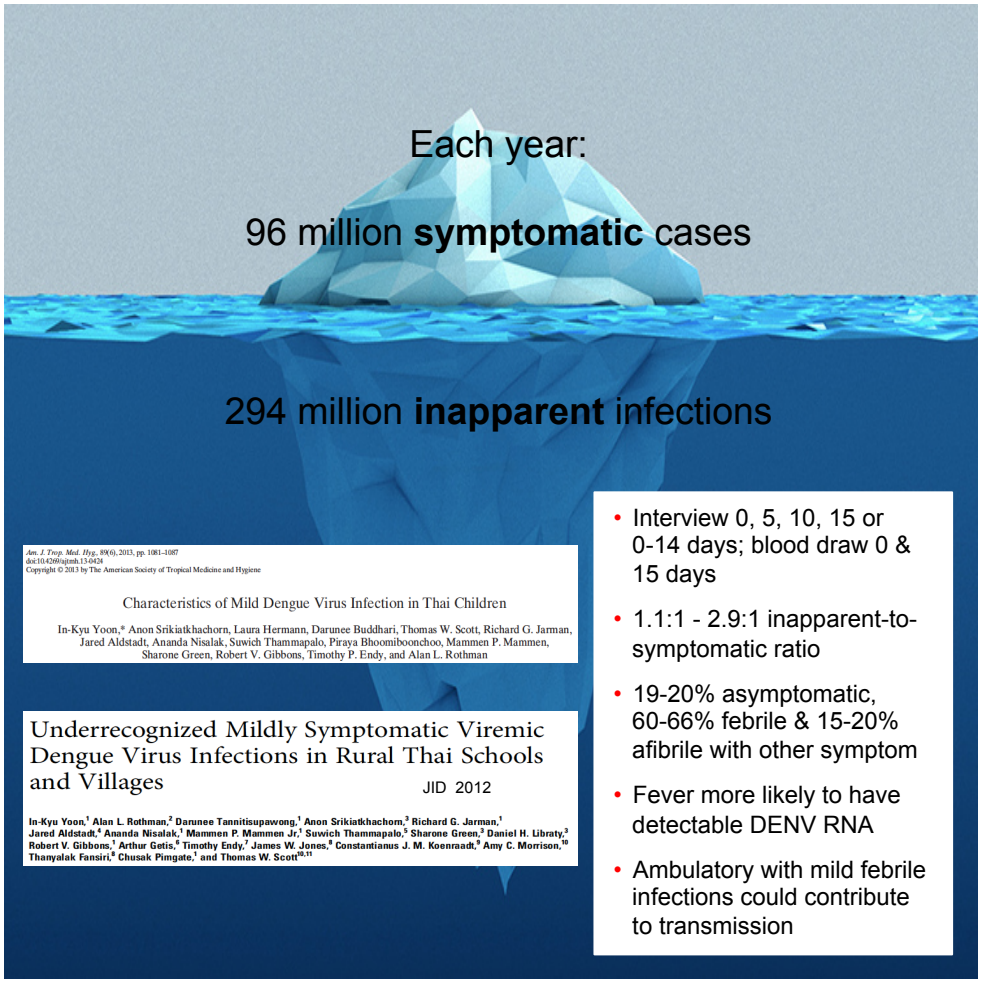
DENV-4
OID_{50}= 7.49

Nguyen et al. *PNAS* 2013

Are Inapparent Infections Dead-End Hosts?

Continuum of Disease

None **Inapparent** **Mild** **Severe**



Bhatt et al. *Nature* 2013

OPEN ACCESS Freely available online PLoS NEGLECTED TROPICAL DISEASES

Determinants of Inapparent and Symptomatic Dengue Infection in a Prospective Study of Primary School Children in Kamphaeng Phet, Thailand 2011

Timothy P. Endy[1]*, Kathryn B. Anderson[2], Ananda Nisalak[3], In-Kyu Yoon[3], Sharone Green[4], Alan L. Rothman[4], Stephen J. Thomas[3], Richard G. Jarman[3], Daniel H. Libraty[4], Robert V. Gibbons[3]

Inapparent: Confirmed infection with insufficient symptoms to be detected by existing surveillance systems and health care providers

Asymptomatic: Confirmed infection in the complete absence of symptoms

- Disease severity positively correlated to viremia level
- Inapparent infections assumed to inefficiently infect mosquitoes
- Dengue outbreaks associated with low viremia

Am. J. Trop. Med. Hyg., 27(3), 1978, pp. 581–589
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EPIDEMIOLOGIC, CLINICAL, AND VIROLOGIC OBSERVATIONS ON DENGUE IN THE KINGDOM OF TONGA

DUANE J. GUBLER, DWAYNE REED,* LEON ROSEN, AND JAMES C. HITCHCOCK, JR.

Am. J. Trop. Med. Hyg., 30(5), 1981, pp. 1094–1099
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EPIDEMIC DENGUE 3 IN CENTRAL JAVA, ASSOCIATED WITH LOW VIREMIA IN MAN*

D. J. GUBLER,† W. SUHARYONO, I. LUBIS, S. ERAM, AND S. GUNARSO

Variation in Human DENV Transmission to Mosquitoes

PNAS
Asymptomatic humans transmit dengue virus to mosquitoes
2015
Veasna Duong[a,1], Louis Lambrechts[b,c,1], Richard E. Paul[c,d], Sowath Ly[e], Rath Srey Lay[a], Kanya C. Long[f], Rekol Huy[g], Arnaud Tarantola[e], Thomas W. Scott[f,h], Anavaj Sakuntabhai[c,d], and Philippe Buchy[a,i,2]

Passive hospital-based surveillance + geographical cluster investigations

Enrollment of **index dengue cases** at 3 hospitals in Kampong Cham province, Cambodia

Enrollment of **cluster participants** in households located <200m from an index case's home

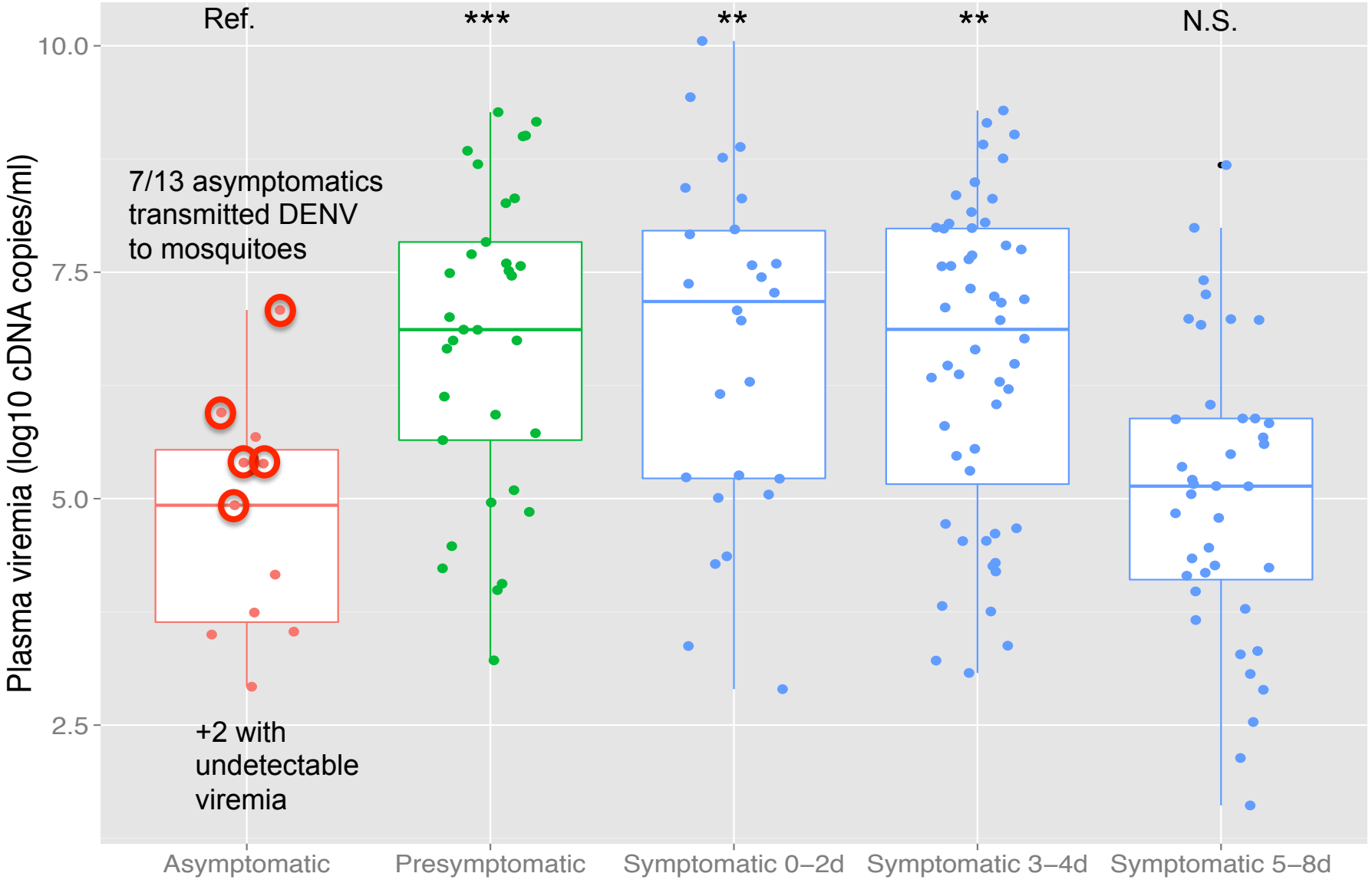
Wild-type, lab-reared *Aedes aegypti* exposed to viremic blood and their legs/wings tested by RTqPCR after 14d

Indirect feeding (≥2yr old)

Direct feeding (≥4yr old)

Active DENV infections detected by NS1 rapid test and RTqPCR. Asymptomatic infections monitored daily for 10d.

Despite Lower DENV Viremia Asymptomatics Can Be Infectious to Mosquitoes



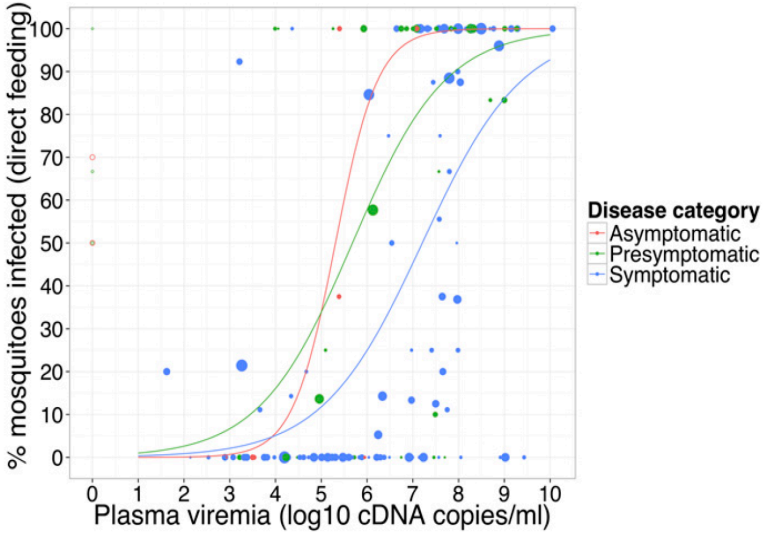
Severity of Disease and Virus Transmission

Continuum of Disease

None **Inapparent** **Mild** **Severe**

Doung et al. 2015 PNAS

- Overall viremia & disease category were associated with likelihood of mosquito infection (not immune status, age, EIP)
- Despite their lower average level of viremia, asymptomatic people can infect mosquitoes
- At a given level of viremia, people with no symptoms (13) or before symptoms (42) more infectious to mosquitoes than people with symptoms (126)
- Infective people without symptoms or before symptoms have the potential to contribute more to transmission than previously recognized



Quantifying Heterogeneities in Dengue Virus Transmission Dynamics (NIH P01AI098670); Iquitos, Peru

- Variation among people in their contribution to transmission (mosquito feeds)
- Epidemiological & sociobehavioral contributions to transmission
- Predict risk & most effective public health measures (modeling)

ZIKA VIRUS INFECTION EXPERIMENTALLY INDUCED IN A HUMAN VOLUNTEER

BY

W. G. C. BEARCROFT*

West African Council for Medical Research Laboratories, Lagos, Nigeria.

TRANSACTIONS OF THE ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE.
Vol. 50. No. 5. September, 1956.

RAPID COMMUNICATIONS

Potential for Zika virus transmission through blood transfusion demonstrated during an outbreak in French Polynesia, November 2013 to February 2014

D Musso (dmusso@ilm.pf)[1], T Nhan[1], E Robin[1], C Roche[1], D Bierlaire[2], K Zisou[1], A Shan Yan[1], V M Cao-Lormeau[1], J Broult[2]
1. Unit of Emerging Infectious Diseases, Institut Louis Malardé, Tahiti, French Polynesia
2. Centre hospitalier du Taaone, Tahiti, French Polynesia

42/1,505 = 3%

Risk of Zika Virus Transmission and Travelers Departing from Brazil

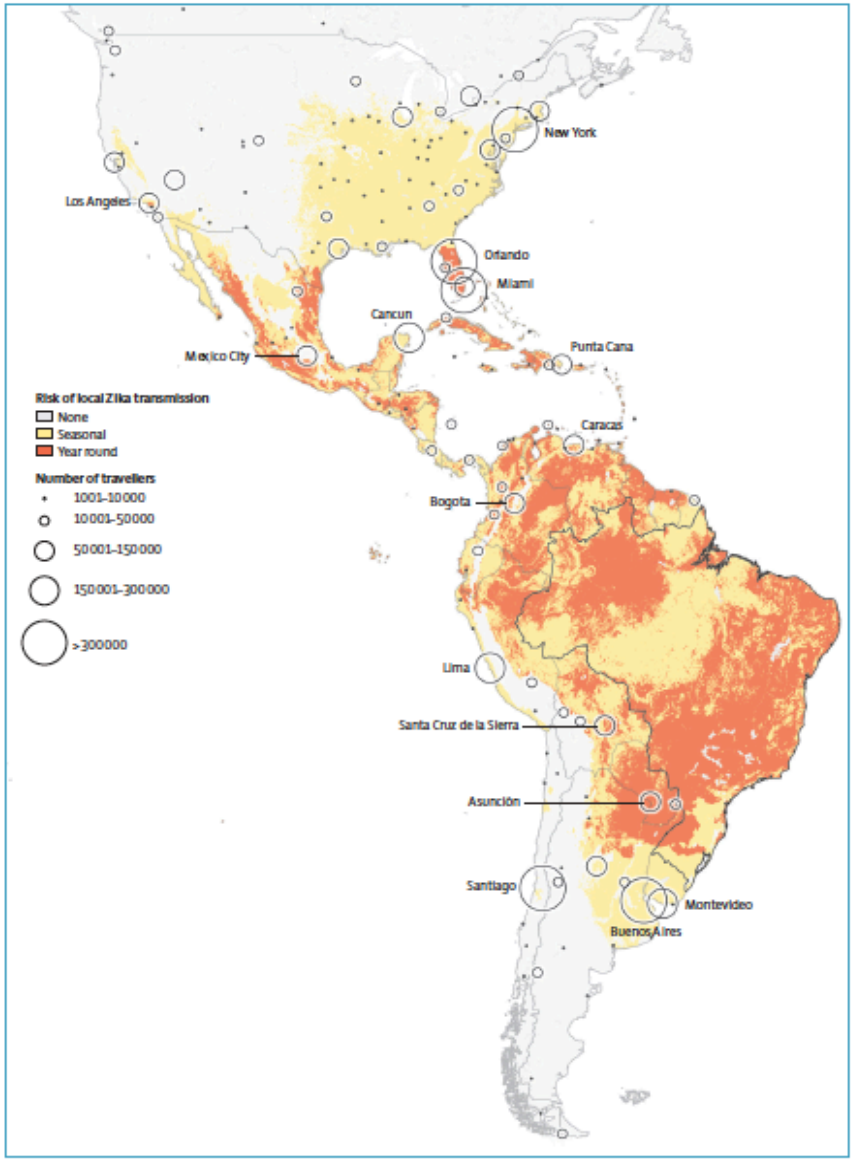
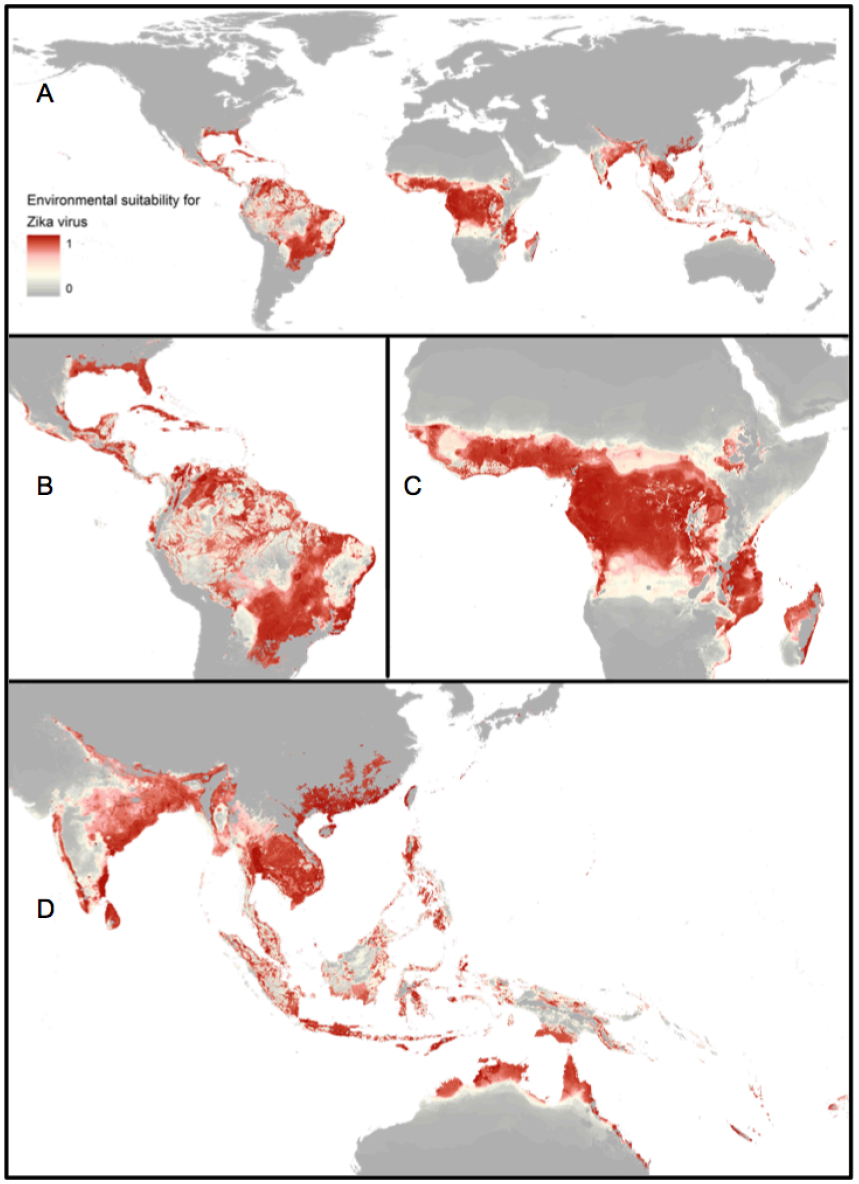


Figure: Final destinations of travellers departing Brazil by potential for autochthonous Zika transmission

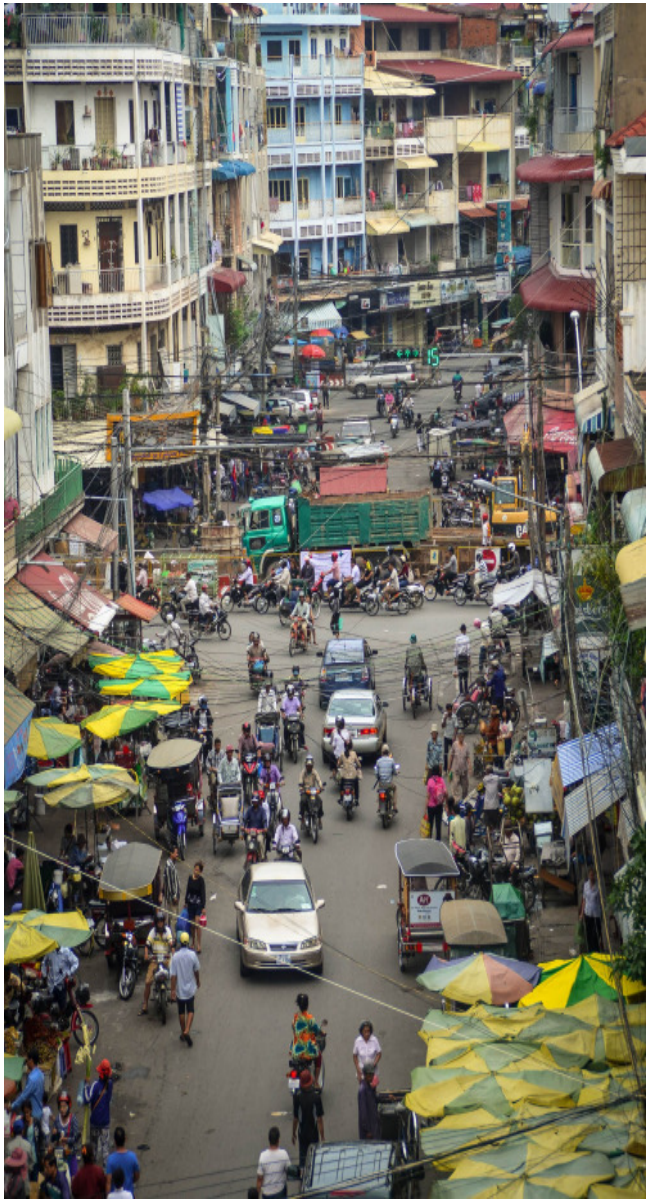
Bogoch et al. 2016. Lancet

Predicted Global Environmental Suitability for Zika Virus



Messina et al. in review

Conclusions and Implications



- An experimental system for quantifying the trajectory of viremia/ infectiousness and relative contribution to transmission of people across the continuum of disease
  - Limitation: Logistically challenging and require rapid detection of viremic/infectious people
- People with asymptomatic/presymptomatic/mild disease flavivirus infections can be infectious to mosquitoes
  - DENV & small sample size (n=13, 7%)
  - Low ZIKV viremia
- Knowledge gap: Role of “silent transmission” in ZIKV epidemiology?
- Relative contribution to transmission needs to be quantified
  - Trajectory of infectiousness
  - Exposure to mosquitoes
  - Lack of symptoms/mild disease may increase risk of human-mosquito encounters (i.e., bites)
- Public health implications:
  - Unrecognized invasion/spread and amplification
  - Reactive (rapid detection and response) vs pre-emptive intervention
  - *Ae. aegypti* control
  - Trial design for assessing efficacy of prevention tools

Vol 454|14 August 2008|doi:10.1038/nature07084 nature

LETTERS

Inapparent infections and cholera dynamics

Aaron A. King[1,2], Edward L. Ionides[3], Mercedes Pascual[1,4] & Menno J. Bouma[5]

Inapparent infections force a more rapid rise and subsequent fall of cholera epidemics, shifting the perceived epidemic peak to an earlier time than previously recognized, and accelerating epidemic transmission and geographic spread.